IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of Porubek *et al.*
Application No.: 08/932,834
Filed: September 19, 1997
Docket No.: 077319/0129
For: **COMPOUNDS HAVING SELECTIVE HYDROLYTIC POTENTIALS**

BRIEF ON APPEAL

Appeal from Group 1611

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Appellants' hereby appeal the November 17, 1998 final rejection of the above-identified application to the Board of Patent Appeals and Interferences.

I. REAL PARTY IN INTEREST

Cell Therapeutics Inc. (CTI), Seattle, WA, owns the entire right, title and interest in the present patent application, as evidenced by an assignment filed on January 6, 1995. CTI is, therefore, the real party in interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of no other appeals or interferences pertaining to the instant invention.

III. STATUS OF CLAIMS

Claims 1, 2, 4, 6, 7, 9, 10, 12-16, 18-21 and 23-27 are pending.[1] A copy of the current claims is presented at APPENDIX I.

IV. SUMMARY OF THE INVENTION

The claims are drawn to compounds that have selective hydrolytic potential, which means that they have varying degrees of stability in different chemical and biological environments (specification, paragraph bridging pages 3 and 4). Moreover, this stability is controlled; *i.e.*, they generally are modified or decompose in a particular, controlled way in certain environments, yielding useful alcohol products (page 4, lines 8-9). For instance, many of the exemplified compounds, in one aspect, can be converted *in vivo* to lisofylline (page 5, lines 35-36), which is useful for a variety of clinical indications (page 1, line 33 to page 2, line 3). All of the compounds within the present claims embody such compounds.

[1] The Examiner indicated in Paper 35, mailed July 29, 1999, that Applicants amendments would be entered upon filing an Appeal Brief.

V. ISSUE ON APPEAL

The sole issue on appeal is whether the specification complies with 35 U.S.C. §112, first paragraph, and provides an enabling disclosure for one of ordinary skill in the art to make and use the invention recited by the claims. See the Office Action dated November 27, 1998 (paper No. 27). The Examiner's rejection derives from two contentions: (1) the doses exemplified in the specification would not enable one to use the present compounds and (2) the compounds of the appealed claims are lisofylline pro-drugs and, since lisofylline is not useful for anything, the claims compounds likewise are not useful.

VI. GROUPING OF THE CLAIMS

Compound claims 1, 2, 4, 6, 7, 9, 10, and 12-14 are patentable even if pharmaceutical composition claims 15, 18-21 and 23-27 are not. The Federal Circuit and its predecessor court, for the purposes of the "how-to-use" aspect of enablement, have consistently treated compound claims differently from claims that recite a therapeutic utility, such as pharmaceutical compositions.

With regard to compound claims, evidence of virtually any credible pharmaceutical activity is sufficient. *See Cross v. Iizuka*, 3 F.2d 1040, 4 USPQ.2d 739 (Fed. Cir. 1985) (*in vitro* pharmacological activity sufficient; distinguishing *In re Gardner*, below, where therapeutic utility was recited in the claims); *In re Bundy*, 642 F.2d 430, 209 USPQ 48 (CCPA 1981) (compound claims enabled in the absence of any data or knowledge about dose; distinguishes *In re Gardner*, on the basis of no claimed therapeutic utility).

On the other hand, in cases where a therapeutic utility is recited in the claims, a somewhat higher standard may pertain. *See In re Gardner*, 166 USPQ 138 (CCPA 1970) (pharmaceutical composition and method claims not enabled where specification did not disclose subject being treated or dosage in terms of body weight); *accord, In re Colianni*, 561 F.2d 220, 195 USPQ 150 (CCPA 1977) (therapeutic method of mending bones not enabled where specification provides no parameters to define "sufficient" ultrasonic energy, deemed crucial to method).

Because the prevailing law enunciates a lower standard for "how-to-use" when considering claims to compounds *per se*, claims 1, 2, 4, 6, 7, 9, 10, 12-14 may be found sufficiently enabled, even if the Board finds that claims 15, 18-21 and 23-27 are not. Accordingly, the former set of claims is separately patentable, relative to the latter set.

VII. SUMMARY OF THE ARGUMENT

A first ground of rejection relates to purportedly confusing language in the specification concerning dose. Since an objective reading of allegedly contradictory passages in the specification reveals that, in fact, there is no contradiction, the specification should not be faulted on this basis. Moreover, given the ample guidance in the specification, including working examples, the skilled artisan would be well-equipped to practice the present invention. Finally, the case law cited by the PTO is not applicable to the claimed compounds, and it is distinguishable from the present compositions.

The second ground of rejection is that the present claims recite compounds that are useful only as precursors to a product, lisofylline, that has no utility. This assertion contravenes Appellants' specification, however, and yet is unsubstantiated by probative evidence or reasoning. Accordingly, the Examiner has not sustained his burden of proof in this context.

VIII. ARGUMENT

A. The Skilled Artisan Would Have No Difficulty Implementing, By Routine Experimentation, The Guidance Provided In The Specification With Regard To Dosage

1. The Specification does not Engender Enablement-Defeating Confusion

Alleged confusion in the specification over proper dosage is not a bar to enablement in this case. The Examiner points to language in the specification as failing to teach the artisan how to use the invention. The relevant passage on dosage reads:

> The daily dosage regimen for **oral administration** is suitably from about 0.1 mg/kg to about 1000 mg/kg per day. For

> **administration** the dosage is suitably from about 0.001 mg/kg to about 40 mg/kg of the inventive compound or a pharmaceutically acceptable salt thereof. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.
>
> While dosage values will vary, therapeutic compounds of the invention may be administered to a human subject requiring such treatment at an effective oral dose of about 50 mg to about 5000 mg per day, depending on the weight of the patient. For any particular subject, specific dosage regimens should be adjusted to the individual's need and to the professional judgement of the person administering or supervising the administration of the inventive compounds.

(Emphasis added.) At first blush, the initial two sentences quoted above seem to recite overlapping dose ranges. It is the Examiner's contention that this apparent inconsistency would render the artisan unable to use the claimed compounds and pharmaceutical compositions. Appellants contest this point on several grounds.

First, it is apparent that the first sentence refers to oral administration; it says "oral administration." On the other hand, the second sentence refers generically to "administration." Objectively, it is apparent that there is a typographical error in the second sentence, and that it should read "non-oral" administration, in contrast with the first sentence.

This view is supported by the fact that the first sentence (oral administration) recites higher doses than the second sentence (generic administration). As explained on page 2 (lines 22-33), orally administered drugs are subject to the so-called "first pass" effect, which results in substantial degradation of orally administered compounds by exposure to the harsh gastric and hepatic environments, the site of high concentrations of inactivating, mixed-function oxidases, before they ever enter the systemic circulation. This is common knowledge.

Related to knowledge of the first pass effect, it is also common knowledge that compounds delivered orally will almost always be administered at higher doses than when delivered parenterally (like intravenous). Thus, one skilled in the art would read this two apparently inconsistent statements consistently with such well-known principles; the first pertaining to oral administration, and the second to non-oral administration.

Moreover, as noted, the first sentence clearly pertains to oral dosage, which is the focus of the pharmaceutical aspects of the invention, and the very next paragraph gives ***oral*** unit dose sizes and frequency of administration. In other words, this discussion which clearly pertains to "oral" administration provides ample guidance to one seeking to use the invention.

2. Irrespective of any Alleged Confusing Guidance, the Specification is Objectively Enabling for Dose

The above-discussed passage of the specification aside, Appellants' disclosure is amply enabling overall. The standard for objectively testing enablement is whether those of skill, given the specification as guidance, would require "undue experimentation" to make and use the claimed invention. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). An appropriate analysis may include consideration of the following: (1) quantity of experimentation necessary; (2) amount of guidance; (3) working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability or unpredictability of the art, and (8) breadth of the claims. *Id.*

The guidance in the specification is ample, including working examples. For instance, Examples 22-25 provide further dosing guidance in both *in vitro* and *in vivo* systems. Notably, each of these models is relevant to the first pass effect, which is a concern in oral administration. These experiments also provide benchmarks for determining dose by determining how much lisofylline is released upon application to a biological environment. Since lisofylline is a known medicament, this guidance is even more than it appears.

Furthermore, in view of the instant specification, generating the clinical data needed to determine suitable dosage requires only the routine experimentation that is endemic to the development of any pharmaceutical agent. Indeed, determining a suitable, non-toxic dosage regimen is a primary purpose of clinical trials. Using standard dose escalation protocols, this determination is routinely made for ***every drug*** undergoing clinical investigation. Accordingly, considering the vast number of drugs that have undergone clinical investigation, there is a ***very high level of skill*** in the pharmaceutical and chemical arts.

In addition, the instant compounds are substituted xanthine derivatives and, in addition to knowledge of lisofylline in particular, the clinician would have experience with substituted xanthines as a class of drugs. See, for example, GOODMAN AND GILMAN'S: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 7th ed., pp. 589-603 (Macmillan Publishing Co., N.Y. 1985). Moreover, the claims as now written uncontrovertibly recite only lisofylline-like compounds. The clinical experience with structurally similar compounds and the high level of skill in the art compels the conclusion that ascertaining a suitable dosage would not require undue experimentation.

3. The case of *In re Gardner*, Proffered by the PTO to Support the Present Rejection, is Inapplicable to Compound Claims and Distinguishable from the Instant Composition Claims

At several points in the prosecution of this rejection, the Examiner has cited *In re Gardner, supra*, in support of this rejection. That case, however, is inapplicable to claims that encompass compounds *per se*. *See Cross v. Iizuka*, 3 F.2d 1040, 4 USPQ.2d 739 (Fed. Cir. 1985) (citing *In re Bundy* and distinguishing compound claims from the therapeutic composition and method claims of *In re Gardner*); *In re Bundy*, 642 F.2d 430, 209 USPQ 48 (CCPA 1981) ("This is not the same situation as in *In re Gardner* .... Here only the compounds themselves are being claimed, not their therapeutic use.") (citation omitted).

Moreover, the facts of *Gardner* are distinguishable from those of the composition claims now on appeal. The problem in *Gardner* was that the specification recited neither a recipient ("host") of the claimed pharmaceutical invention nor any dosage in terms of body weight, volume, or any other ascertainable standard. 166 USPQ at 140-41. Such is not the problem in the present case, where, as described above, there is ample dosing information. Moreover, the present claims represent precursors of lisofylline, a known medicament, and the specification particularly points to that compound and its therapeutic uses (page 1, last paragraph), familiar items to the knowledgeable reader. This explicit teaching by Appellants is unlike the newly discovered pharmacological activity of *Gardner*, a case where the applicant tried on appeal to generalize, without foundation in the specification, from dosage for a "standard" compound in the art to that of the claimed composition. 166 USPQ at 141.

B. The Examiner Has Not Sustained The PTO's Burden Of Proof By Asserting, Inaccurately, That Lisofylline Itself Is Not Useful And, Hence, That The Skilled Person Could Not Use The Claimed Lisofylline Precursors

Finally, the Examiner contends that Appellants "have not presented evidence that lisofylline has actually been shown useful for anything." Thus, the Examiner's reasoning appears to be: (a) the instant compounds are prodrugs of lisofylline; (b) the sole usefulness of the inventive compounds is as lisofylline prodrugs; and, therefore, (c) lisofylline is not "useful for anything" and, likewise, (d) the present compounds are not "useful for anything."

Appellants' specification expressly teaches that the presently recited compounds are useful as prodrugs of lisofylline, although other utilities also are described. Additionally, the specification details the usefulness of lisofylline. Yet the Examiner proffers no evidence whatsoever to support his contrary proposition, namely, that the recited compounds lack utility because lisofylline itself is ***useless***. In other words, the Examiner's rationale for this rejection resolves to a bald statement that "I do not believe you." This is insufficient, as a matter of law.

It is well settled that, during prosecution, an applicants' specification is deemed enabling, absent findings by the Examiner to the contrary. *In re Wright*, 27 USPQ2d 1510 (Fed Cir. 1993). Indeed, as stated by the court in *In re Marzocchi*,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain to explain <u>why</u> it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to trouble and expense of supporting his presumptively accurate disclosure. [169 USPQ 367, 370 (CCPA 1971).]

By the same token, Appellants enjoy a presumption of enablement that must be rebutted with "evidence or reasoning," and a failure to rebut this presumption means that their specification is enabling as a matter of law. Thus, the Examiner contests the presumption of enablement without putting forward any supporting evidence. Rather, he purports to shift the

burden by means of conclusory statement, effectively imposing a presumption of non-enablement. This is improper.

Supplementing the specification, the declaration of Dr. Carolyn Paradise sets out the results of clinical investigations, using lisofylline, which demonstrate that lisofylline indeed is useful for something. By submitting the Paradise declaration, Appellants have gone beyond what is required and adduced evidence of utility/enablement. The rejection in question should be reversed, in view of this evidence and the Examiner's failure to sustain the PTO's burden of substantiating non-enablement.

IX. CONCLUSION

Accordingly, Appellants respectfully solicit the Honorable Board of Patent Appeals and Interferences to reverse the rejections of the pending claims and pass this application on to allowance.

Respectfully submitted,

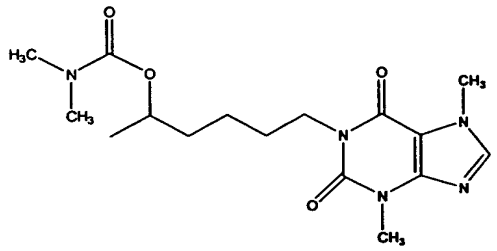
1 October 1999
Date

for Reg. No. 42,822
Stephen A. Bent
Registration No. 29,768

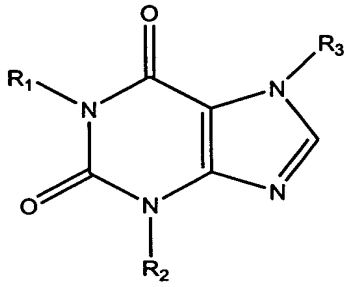
APPENDIX I

The claims are presented below as amended, since the Examiner indicated that Applicants amendments would be allowed upon submission of their Brief.

1. A compound having the following structure:



or a structure according to formula I:



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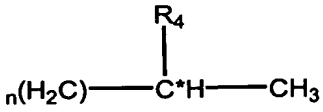
wherein R_1 has the formula II:



R_2 and R_3 are independently $C_{(1-12)}$ alkyl, optionally, R_2 having one or two nonadjacent carbon atoms of the $C_{(1-12)}$ alkyl being replaced by an oxygen atom; and wherein:

C* is a chiral carbon atom;

n is four;

R_4 is a naturally occurring amino acid or a carbohydrate-moiety attached by an oxygen atom to the chiral carbon atom C* by an ester linkage, or -O-X-$(R_5)_m$; m being two or three, depending on valence, and X being selected from the group consisting of C, P or S; wherein one R_5 is =O and any other R_5 is a member independently selected from Group Q,

said carbohydrate moiety is selected from the group consisting of glucosyl, glucosidyl, maltosyl, glucopyranosidyl, glyceraldehydyl, erythrosyl, arabinosyl, ribolucosyl, fructosyl, erythritolyl, xylosyl, lyxosyl, allosyl, altrosyl, mannosyl, mannosidyl, gulosyl, idosyl, galactosyl and talosyl, and

Group Q consists of:

hydroxyl group;

substituted or unsubstituted $C_{(3-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, $C_{(1-10)}$ carboxyalkyl, $C_{(1-10)}$ hydroxyalkyl, or substituted $C_{(1-2)}$ alkyl group;

$-OR_6$, R_6 being a substituted or unsubstituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, or $C_{(1-10)}$ oxoalkyl;

substituted or unsubstituted heterocylic group, attached to X through an atom within the ring, having one or two rings, each ring containing from four to seven atoms, wherein the heteroatom(s) of said heterocyclic group is 1 or 2 nitrogens; and

substituted or unsubstituted carbocyclic group that is attached to X through a carbon atom within a ring, having one or two rings, each ring containing four to seven atoms, wherein the substituents of said substituted carbocyclic group are selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, hydroxyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(2-6)}$ mono- or di-haloalkyl, isocyano, isothiocyano, imino, a chlorine atom, a bromine atom, a fluorine atom and an oxygen atom.

2. The compound of claim 1, wherein the amino acid is selected from the group consisting of: alaninyl, argininyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glycinyl, histidinyl, isoleucinyl, leucinyl, lysinyl, methioninyl, phenylalaninyl, prolinyl, serinyl, threoninyl, tryptophanyl, tyrosinyl and valinyl.

4. The compound of claim 1, wherein X is C.

6. The compound of claim 1, wherein substituents for the substituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, or heterocylic groups selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(1-6)}$ haloalkyl, isocyano, isothiocyano, imino, alkylthio, or a chlorine, bromine, fluorine and oxygen atom.

7. The compound of claim 6, wherein the $C_{(1-6)}$ haloalkyl is a mono-, di- or tri haloalkyl and the $C_{(1-6)}$ alkoxyl is a methoxy or ethoxy group.

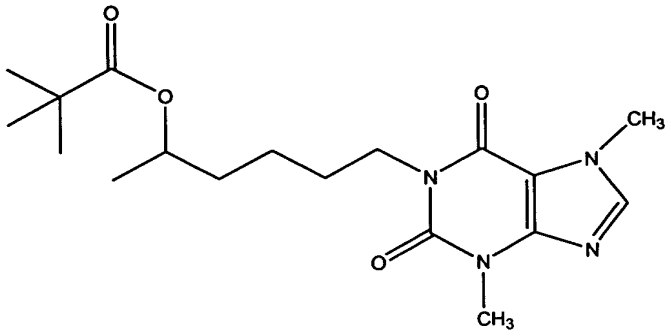
9. The compound of claim 1, wherein the R_1 or R_2, other than formula II, contains one or two, nonadjacent oxygen atoms, each oxygen atom replacing a single carbon atom of the $C_{(1-12)}$ alkyl.

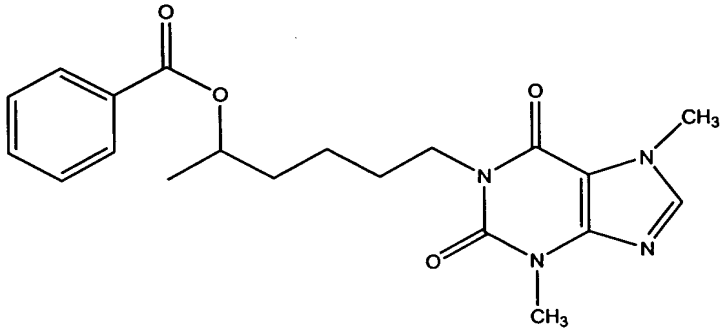
10. The compound of claim 1, wherein the carbocyclic or heterocyclic group is selected from the group consisting of benzyl, phenyl, biphenyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, cyclopentanedionyl, napthlalenyl, phenolyl, quinonyl, cyclobutyl, cycloheptyl, cycloheptenyl, indanyl, indenyl, decalinyl, resorcinolyl, tetralinyl, α-tetralonyl, 1-indanonyl, cyclohexanedionyl, cyclopentanedionyl, dimethylxanthinyl, methylxanthinyl, phthalimidyl, homophthalimidyl, quinazolinonyl, glutarimidyl, piperidonyl, succinimidyl, dimethoxyphenyl, methyldihydrouracilyl, methyluracilyl, methylthyminyl, piperidinyl, dihydroxybenzenyl, methylpurinyl, methylxanthinyl and dimethylxanthinyl.

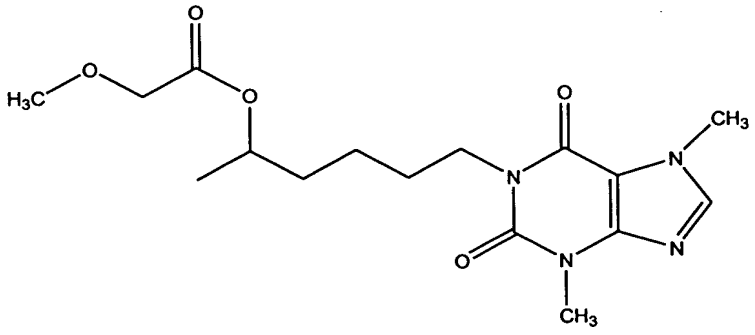
12. (Three Times Amended) The compound of claim 11, wherein the other R_5, other than =O, is trimethoxy-substituted phenyl.

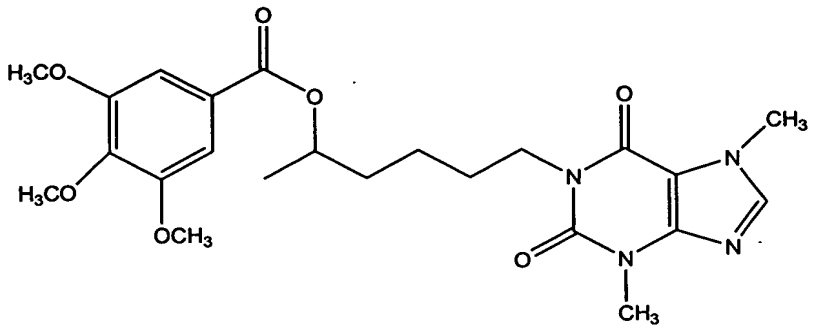
13. The compound of claim 1, wherein R_4 is glycinyl, isoleucinyl or valinyl.

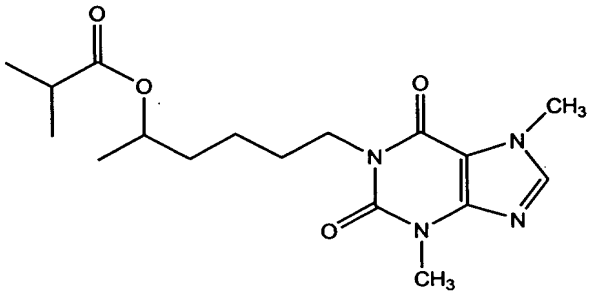
14. The compound of claim 1, wherein said compound is selected from:

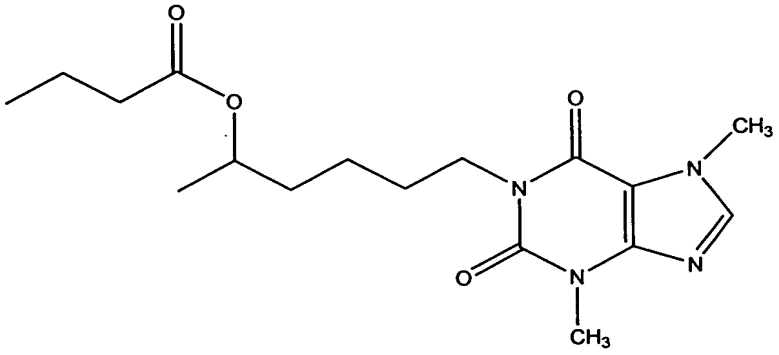


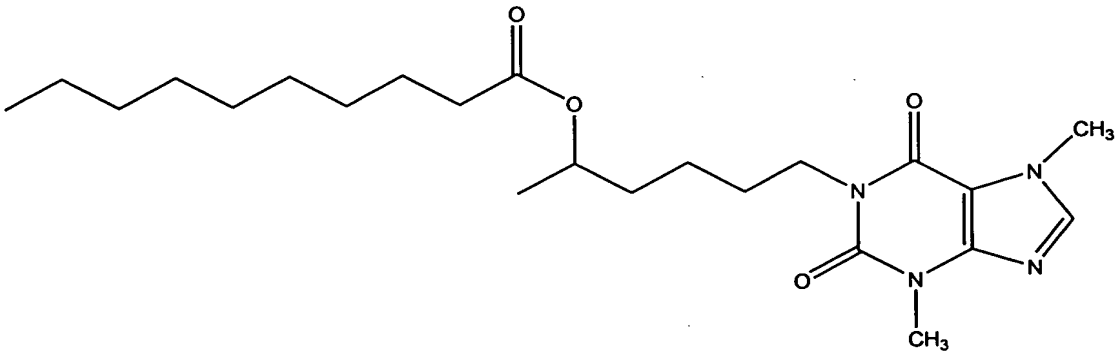


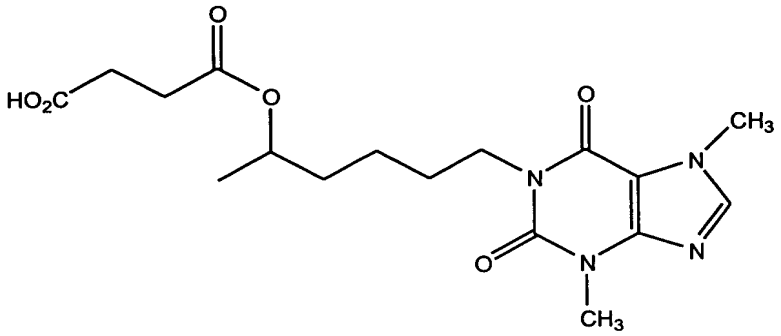


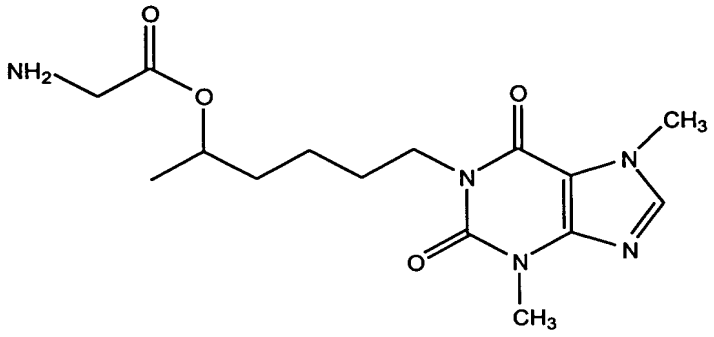


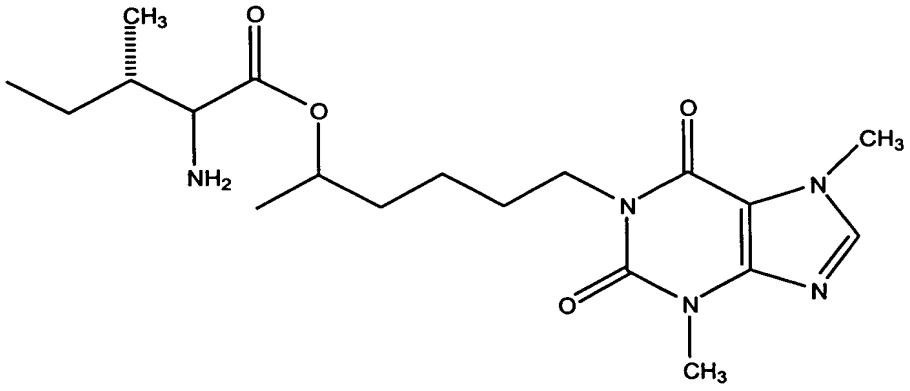


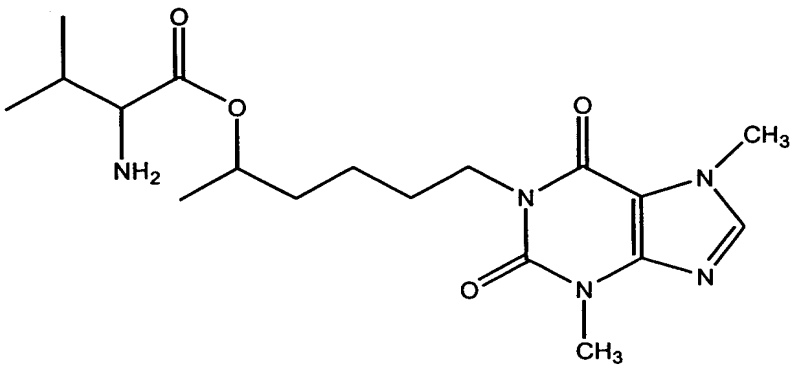


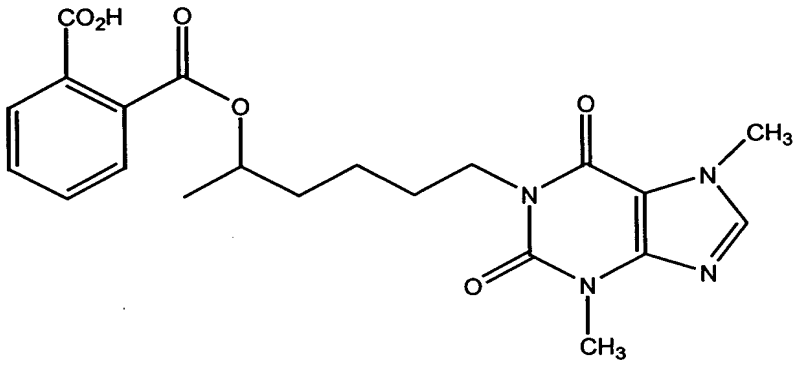


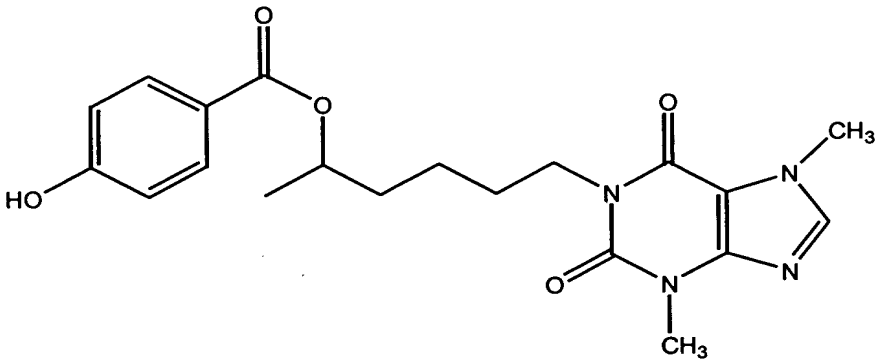


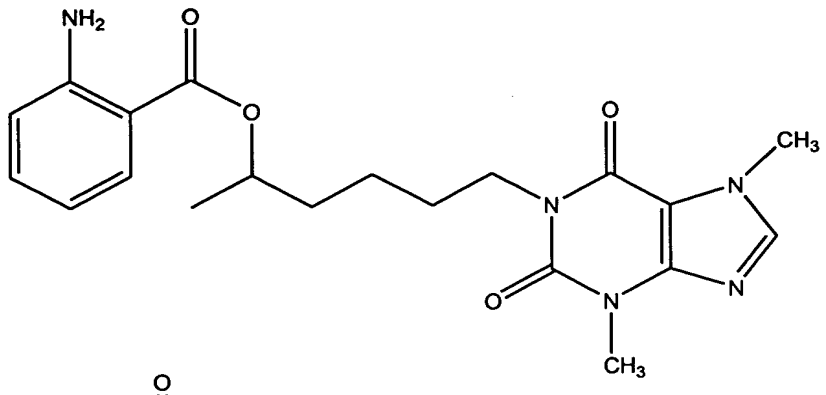


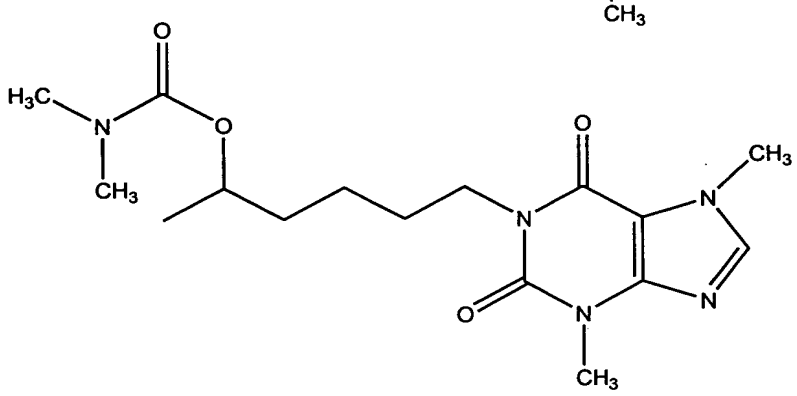












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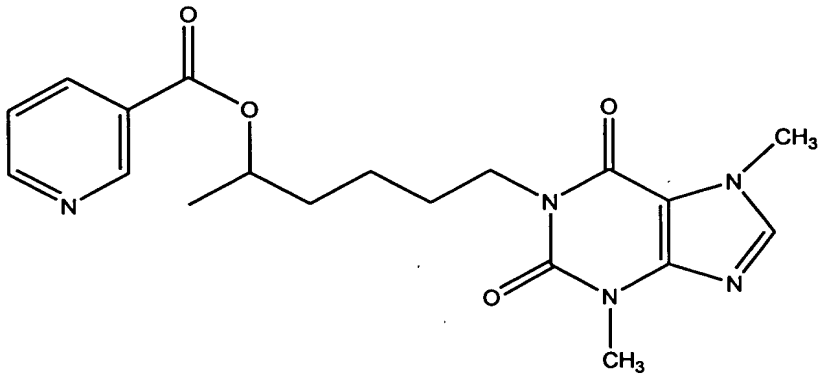
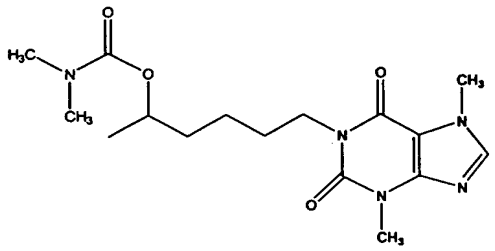
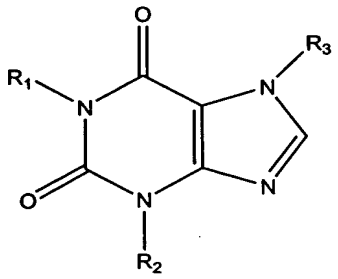


15. A pharmaceutical composition comprising a pharmaceutically acceptable excipient or carrier and a compound having the following structure:



or a structure according to formula I:



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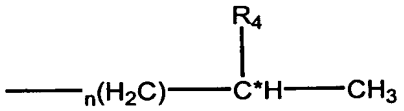
wherein R_1 has the formula II:



R_2 and R_3 are independently $C_{(1-12)}$ alkyl, optionally, R_2 having one or two nonadjacent carbon atoms of the $C_{(1-12)}$ alkyl being replaced by an oxygen atom; and wherein:

C* is a chiral carbon atom;

n is four;

R_4 is a naturally occurring amino acid or a carbohydrate-moiety attached by an oxygen atom to the chiral carbon atom C* by an ester linkage, $-O-X-(R_5)_m$; X being selected from the group consisting of C, P or S; m being two or three, depending on valence, and X being selected from the group consisting of C, P or S; wherein one R_5 is =O and any other R_5 is a member independently selected from Group Q,

said carbohydrate moiety is selected from the group consisting of glucosyl, glucosidyl, maltosyl, glucopyranosidyl, glyceraldehydyl, erythrosyl, arabinosyl, ribolucosyl, fructosyl, erythritolyl, xylosyl, lyxosyl, allosyl, altrosyl, mannosyl, mannosidyl, gulosyl, idosyl, galactosyl and talosyl, and

Group Q consists of:

hydroxyl group;

substituted or unsubstituted $C_{(3-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, $C_{(1-10)}$ carboxyalkyl, $C_{(1-10)}$ hydroxyalkyl, or substituted $C_{(1-2)}$ alkyl group;

$-OR_6$, R_6 being a substituted or unsubstituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, or $C_{(1-10)}$ oxoalkyl;

substituted or unsubstituted heterocylic group, attached to X through an atom within the ring, having one or two rings, each ring containing from four to seven atoms, wherein the heteroatom(s) of said heterocyclic group is 1 or 2 nitrogens; and

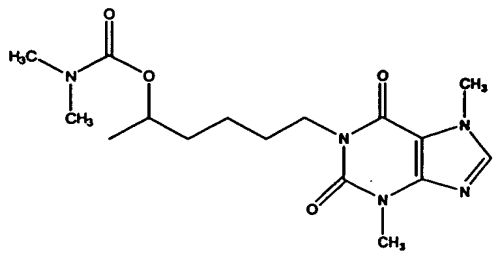
substituted or unsubstituted carbocyclic group that is attached to X through a carbon atom within a ring, having one or two rings, each ring containing four to seven atoms, wherein the substituents of said substituted carbocyclic group are selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, hydroxyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(2-6)}$ mono- or di-haloalkyl, isocyano, isothiocyano, imino, a chlorine atom, a bromine atom, a fluorine atom and an oxygen atom.

16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is formulated for oral administration.

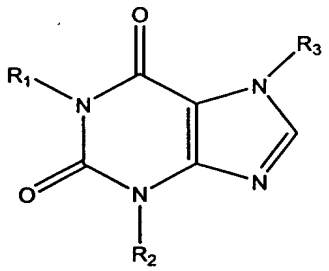
18. (Amended) The pharmaceutical composition of claim 15, wherein R_5 is trimethoxy-substituted phenyl.

19. The pharmaceutical composition of claim 15, wherein R_4 is glycinyl, isoleucinyl or valinyl.

20. (Four Times Amended) A compound having the following structure:

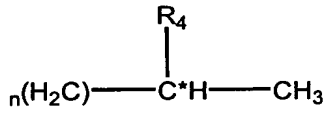


or a structure according to formula I:



I

wherein R_1 or R_2 has the formula II:



R_1 or R_2, which is other than formula II, and R_3 are independently $C_{(1-12)}$ alkyl, optionally, R_2 having one or two nonadjacent carbon atoms of the $C_{(1-12)}$ alkyl being replaced by an oxygen atom; and wherein:

C* is a chiral carbon atom;

n is four;

R_4 is a naturally occurring amino acid or a carbohydrate-moiety attached by an oxygen atom to the chiral carbon atom C* by an ester linkage, -O-X-$(R_5)_m$; m being two or three depending on valence, and X being selected from the group consisting of C, P or S; wherein one R_5 is =O and any other R_5 is a member independently selected from Group Q,

said carbohydrate moiety is selected from the group consisting of glucosyl, glucosidyl, maltosyl, glucopyranosidyl, glyceraldehydyl, erythrosyl, arabinosyl, ribolucosyl, fructosyl, erythritolyl, xylosyl, lyxosyl, allosyl, altrosyl, mannosyl, mannosidyl, gulosyl, idosyl, galactosyl and talosyl, and

Group Q consists of:

hydroxyl group;

substituted or unsubstituted $C_{(3-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, $C_{(1-10)}$ carboxyalkyl, $C_{(1-10)}$ hydroxyalkyl, or substituted $C_{(1-2)}$ alkyl group;

$-OR_6$, R_6 being a substituted or unsubstituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, or $C_{(1-10)}$ oxoalkyl;

substituted or unsubstituted heterocylic group, attached to X through an atom within the ring, having one or two rings, each ring containing from four to seven atoms, wherein the heteroatom(s) of said heterocyclic group is 1 or 2 nitrogens; and

substituted or unsubstituted carbocyclic group that is attached to X through a carbon atom within a ring, having one or two rings, each ring containing four to seven atoms, wherein the substituents of said substituted carbocyclic group are selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, hydroxyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(2-6)}$ mono- or di-haloalkyl, isocyano, isothiocyano, imino, a chlorine atom, a bromine atom, a fluorine atom and an oxygen atom.

21. A compound according to claim 1, wherein R_2 and R_3 are methyl, and wherein R_6 is a

substituted or unsubstituted $C_{(1-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, or $C_{(1-10)}$ oxoalkyl;

substituted or unsubstituted heterocylic group, attached to X through an atom within the ring, having one or two rings, each ring containing from four to seven atoms, and a single nitrogen as the heteroatom; or

substituted or unsubstituted carbocyclic group that is attached to X through a carbon atom within a ring, having one ring containing four to seven atoms, wherein the substituents of said substituted carbocyclic group are selected from the group consisting of amino, $C_{(2-6)}$ alkenyl, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxyl, $C_{(1-6)}$ hydroxyalkyl, hydroxyl, $C_{(1-6)}$ oxoalkyl, azido, cyano, $C_{(2-6)}$ mono- or di-haloalkyl, isocyano, isothiocyano, imino, a chlorine atom, a bromine atom, a fluorine atom and an oxygen atom.

23. A compound according to claim 1, wherein R_3 is methyl.

24. A compound according to claim 23, wherein R_2 is methyl.

25. A compound according to claim 24, wherein X is S.

26. A compound according to claim 25, wherein members of Group Q are independently selected from the group consisting of an hydroxyl group; substituted or unsubstituted $C_{(3-10)}$ alkyl, $C_{(2-10)}$ alkenyl, $C_{(2-10)}$ alkynyl, $C_{(1-10)}$ alkoxyl, $C_{(1-10)}$ oxoalkyl, $C_{(1-10)}$ carboxyalkyl, $C_{(1-10)}$ hydroxyalkyl; and a substituted $C_{(1-2)}$ alkyl group.

27. A compound according to claim 26, wherein the other R_5 is OH.